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EFFECT OF BISOLVON ON THE SURFACE-ACTIVE SUBSTANCE OF THE RAT LUNG

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Effect of Bisolvon on the surface-active substance of the rat lung

by

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There are three conceivable ways in which the surface-active substance in the lung can be influenced by a drug:

1. The direct influencing of the surface film in its composition or in the composition of its hypophase,

2. the indirect influencing of the surface film by substances which are released by the drug, and

3. the influencing of the metabolism of the surface-active substance.

We investigated the influence of N-cyclohexyl-N-methyl-(2-amino-3,5-dibrom benzyl)-ammonium chloride (Bisolvon) on the surface-active substance of the rat lung. The study was divided into measurements in vitro and measurements in vivo. The process of investigation and methodology were reported in detail elsewhere (1).

Results.

I. Studies in vitro.

1. Surface properties of Bisolvon:

The static surface tension of Bisolvon in 0.2% solution measured in Langmuir cup was 65 dyn/cm, the surface tension of the solvent 73 dyn/cm. Bisolvon formed no surface films on the interface hypophase/air.

2. Influencing surface films in Langmuir cup:

In Langmuir cup in hypophases of 0.2% Bisolvon, films of surface-active substance from rat lungs showed an average lowering of the initial static tension by 10 dyn/cm: upon expansion of the film an average lowering

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of the maximal surface tension by 9 dyn/cm and upon compression of the film to 20% of its initial surface an average minimal increase of surface tension by 8 dyn/cm. These changes can be explained easiest by the fact that the static surface tension of the Bisolvon hypophase, which is lower compared to Ringer solution, influences the spreading of the surface film.

Correspondingly, when an 0.02% Bilsolvon hypophase is used, these changes can no longer be demonstrated.

3. Influencing the alveolar mechanics:

Neither after bronchial rinsing with 0.2% Bisolvon solution nor after 15-minute application of an 0.2% Bisolvon aerosol did static pressure volume (pV) diagrams of 14 isolated rat lungs show any changes of the surface forces which could be attributed to the drug.

II. Experiments in vivo.

After 3-day feeding of Bisolvon to 23 rats (control group: 25 animals) in the extremely high dose of 200 mg/kg/day we investigated:

1. Amount of surface-active substance that could be rinsed out.

After preliminary treatment with Bisolvon employing bronchial rinsing we were able to obtain on the average 1.16 mg of organic substance/g lung moist weight. The corresponding value in the control animals was 1.19 mg/g lung moist weight.

2. Lipid phosphate content of the surface-active substance:

The lipid phosphate content as a measure for the content of surface-active phospholipids was 7.1± 0.52 µg/mg of surface-active substance (always mean value ± mean error of the mean value) for preliminarily treated animals and 6.4 ± 0.04 µg/mg substance for the controls.

3. Lipid phosphate content in the lung tissue:

In the lung tissue of the preliminarily treated animals we determined a lipid phosphate content of 0.92 ± 0.02 mg/g lung moist weight, and 0.89 ± 0.01 mg/g lung moist weight in the control animals. Hence, a statistically significant quantitative influence of Bisolvon on the phospholipid metabolism was not demonstrable.

4. Behavior of surface-active substance in Langmuir cup:

Figure 1 and 2 show the results of the study in the Langmuir cup of surface-active substance obtained from lungs of pretreated animals. In comparison to surface/surface tension diagrams of the material of untreated animals we found lowered initial static tensions (γ_{stat}), lowered minimal (γ_{min}) and maximal (γ_{max}) surface tensions and enlarged hysteresis surfaces. These findings suggest an altered activity of the surface-active substance after preliminary treatment with Bisolvon. The altered activity might be the consequence of the changed quantity or changed composition of the surface-active substance. While we could not demonstrate quantity differences, we found a changed ratio of the parameters $\gamma_{max} - \gamma_{min}/\gamma_{min}$. This is an indication of a changed composition of the material after preliminary treatment with Bisolvon. From our studies it cannot be stated how this changed activity of the material following preliminary treatment with Bisolvon acts on the function of the surface-active substance in the lungs.

5. Influences on the alveolar mechanics:

After preliminary treatment with Bisolvon for three days we found no changes in the isolated lungs in the static pV diagrams that would suggest altered surface forces.

In studies in vitro and in vivo in the animal experiment we thus found no indication of a damage of the surface-active substance caused by Bisolvon. The activity change of the surface-active material from rat lungs found after application of extremely high doses might be an indication that the metabolism of the surface-active substance is influenced by Bisolvon. The question of the influence of Bisolvon on the metabolism cannot be answered from our studies, however.

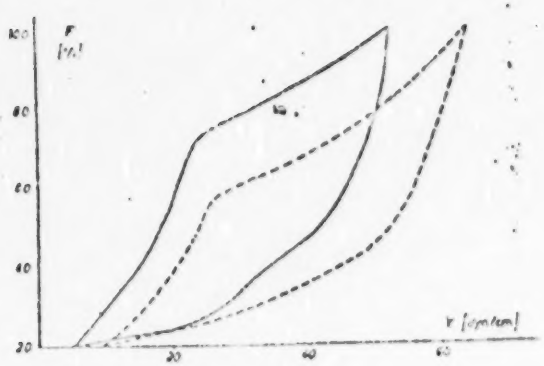

Abb. 1

Flächen/Oberflächenspannungsdiagramme oberflächenaktiver Substanz aus Rattenlungen ohne (- - - -) und nach (———) dreitägiger Behandlung mit Bisolven (200 mg kg/Tag). Die aufgetragene Dosis enthält jeweils 3 µg Lipidphosphat. Auf der Ordinate die Fläche, auf der Abszisse die Oberflächenspannung. (Aus Arzneim.-Forsch. [Drug Res.], 19, 91-96, 1969)

Figure 1. Surface/surface tension diagrams of surface-active substance from rat lung without (----) and after (———) 3-day treatment with Bisolven (200 mg/kg/day). The plotted dose always contains 3 µg lipid phosphate.
Ordinate: surface
Abscissa: surface tension (From Arzneim Forsch 19:91-96, 1969)

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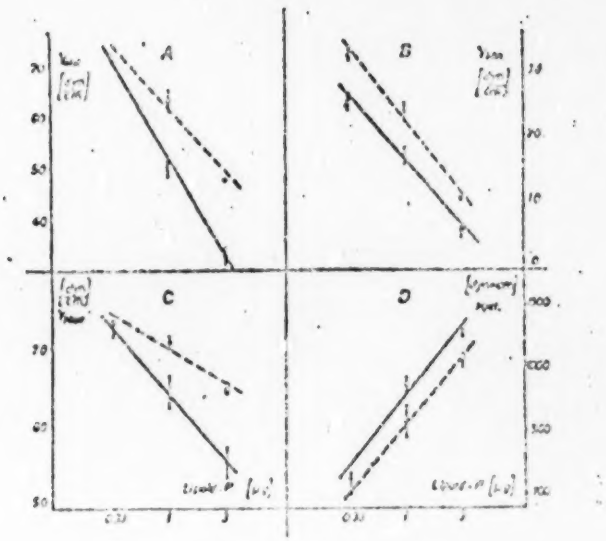

Abb. 2

Auswertung der Flächen/Oberflächenspannungsdiagramme oberflächenaktiver Substanz aus Rattenlungen ohne (- - - -) und nach (——) dreitägiger Behandlung mit Bisolvon (200 mg/kg/Tag). Jeweils Mittelwert ± mittlerer Fehler des Mittelwertes. Auf der Ordinate jeweils die Aktivitätskennzahl. Im: A: Statische Ausgangsspannung; B: Minimale Oberflächenspannung; C: Maximale Oberflächenspannung; D: Hysteresefläche. Auf der Abszisse logarithmisch die aufgetragene Dosis in µg Lipoid-Phosphat. (Aus Arzneim.-Forsch. [Drug. Res.], 19, 91-96, 1969)

Figure 2. Evaluation of the surface/surface tension diagrams of surface-active substance from rat lungs without (----) and after (——) 3-day treatment with Bisolvon (200 mg/kg/day). Always mean value ± mean error of the mean value.
Ordinate: always the characteristic magnitudes of activity;
A: initial static tension; B: minimal surface tension; C: maximal surface tension; D: hysteresis surface.
Abscissa: logarithmically plotted dose in µg lipid phosphate
(From Arzneim Forsch 19:91-96, 1969).

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Literatur:

1. Rafer, R., Lingelbach, E., Schoedel, W., u. Stolz, Chr.: Der Einfluß von N-Cyclohexyl-N-methyl-(2-amino-3,5-dibrom-benzyl)-ammonium-chlorid auf die oberflächenaktive Substanz der Lunge. Arzneim.-Forsch. (Drug Res.) 19, 51-55 (1969).

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J.Chapin, translator
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